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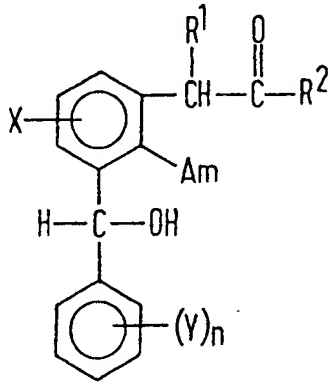
(54) 2-Amino-3-[Hydroxy(phenyl)-methyl]phenylacetic acids, esters and amides

(57) 2-Amino-3-[hydroxy(phenyl)-methyl]phenylacetic acids, metal salts and hydrates thereof, esters and amides having the formula:



are disclosed wherein R^1 represents a hydrogen atom or a loweralkyl group; R^2 represents an $-OH$, $-OM$, $-O-$loweralkyl or $-NR^3R^4$ group; R^3 and R^4 represents a hydrogen atom or a loweralkyl, cycloalkyl or phenyl group, or a phenyl group substituted by one or more loweralkyl, loweralkoxy, or trifluoromethyl groups or halogen atoms an R^3 and R^4 taken together with the adjacent nitrogen may form a heterocyclic residue; M represents a pharmaceutically acceptable cation or fraction thereof when the cation is multivalent; Am represents a primary amino or dimethylamino group; X represents a hydrogen or a halogen atom or a loweralkyl or trifluoromethyl group, Y represents a hydrogen or halogen atom or a lower alkyl, loweralkoxy, trifluoromethyl or methylthio group; and n is 1 to 3 inclusive and when n is greater than one, Y may be the same or different and hydrates of all such compounds. The compounds have *anti-inflammatory, anti-pyretic, analgesic* and *blood-platelet-aggregation-inhibiting activities.*

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Certain of the chemical formulae appearing in the printed specification were submitted after the date of filing, the formulae originally submitted being incapable of being satisfactorily reproduced

SPECIFICATION

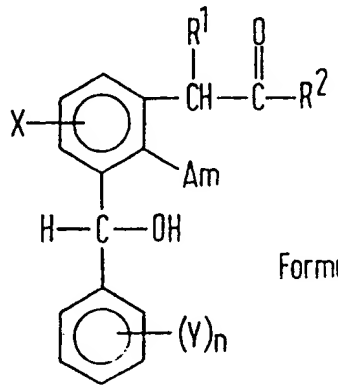
2-amino-3-[hydroxy(phenyl)methyl] phenylacetic acids, st rs and amid s

The present invention relates to 2-amino-3-[hydroxy(phenyl)methyl]phenylacetic acids, metal salts and hydrates thereof, esters and amides which have pharmacological activity in warm-blooded animals and pharmaceutical methods and compositions utilizing the same.

2-Amino-3-(5 and 6) benzoylphenylacetic acids, esters, metal salts and hydrates having anti-inflammatory activity are disclosed in U.S. Patent 4,045,576 and 4,126,635.

South African patent 68/4682 discloses benzoyl-phenylacetamides generically having a variety of substituents in indefinite positions on the phenyl group. None of the specific compounds disclosed therein are aminophenylacetamides.

The compounds of the present invention are 2-amino-3-[hydroxy(phenyl)methyl]phenylacetic acids, metal salts and hydrates thereof, esters and amides illustrated generally by the following formula:



Formula I

wherein;

R^1 represents a hydrogen atom or a lower alkyl group,

R^2 represents an OH, OM, -O-loweralkyl, $-NR^3R^4$ group, R^3 and R^4 represent hydrogen atoms or loweralkyl cycloalkyl, phenyl groups or phenyl groups substituted by loweralkyl, loweralkoxy, halogen, or trifluoromethyl groups and R^3 and R^4 taken together with the adjacent nitrogen may form a heterocyclic residue,

M represents a pharmaceutically acceptable cation of fraction thereof when the cation is multivalent,

Am represents a primary amino ($-NH_2$), or dimethyl-amino group,

X represents a hydrogen or a halogen atom or a loweralkyl or trifluoromethyl group,

Y represents a hydrogen, or a halogen atom or a loweralkyl, loweralkoxy, trifluoromethyl or methylthio group, and n is 1 to 3 inclusive, and when n is greater than one, Y may be the same or different, and hydrates of all the above.

In the further definition of symbols in the formulas hereof and where they appear elsewhere throughout this specification the terms have the following significance:

The term "loweralkyl" as used herein means straight and branched chain radicals of up to eight carbon atoms inclusive and is exemplified by such groups as methyl, ethyl, propyl, isopropyl, butyl, sec. butyl, tertiary butyl, amyl, isoamyl, hexyl, heptyl and octyl radicals. The term "loweralkoxy" means -O-loweralkyl.

The term "cycloalkyl" as used herein means cyclic alkyl radicals containing 3 to 9 carbon atoms inclusive and includes such groups as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylcyclohexyl, and cycloheptyl.

The term "halogen" when referred to herein includes fluorine, chlorine, bromine and iodine, and preferably fluorine, chlorine and bromine.

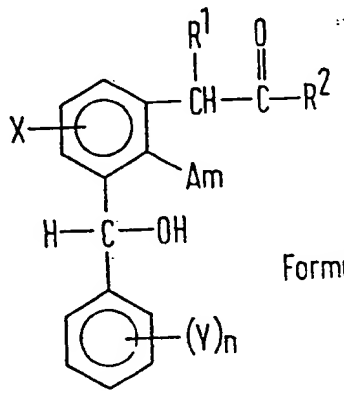
The term "heterocyclic residue" includes radicals such as morpholino, pyrrolidino, piperidino, and piperazino.

The term "pharmaceutically acceptable cation" forming salts of the acids and hydrates and thereof when referred to herein includes any metal cation acceptable for internal administration to warm-blooded animals as exemplified by sodium, potassium, calcium, magnesium, zinc, copper and aluminium and water of hydration. The sodium cation is preferred.

Anti-inflammatory activity was demonstrated in laboratory animals using a modification of the Evans Blue Carrag enan Pleural Effusion Assay of Sancilio, L.F., J. Pharmacol. Exp. Ther. *168*, 199-204 (1969).

The compounds also have application as anti-pyretics, analgesics and in inhibiting blood-platelet aggregation.

Compounds preferred for their anti-inflammatory activity have th formula:



Formula I-1

wherein;

R^1 represents a hydrogen atom or a methyl group,

R^2 represents an -OH, OM, or O-loweralkyl group,

Am represents an $-NH_2$ or di-methylamino group,

X represents a hydrogen or a halogen atom or a loweralkyl, or trifluoromethyl group,

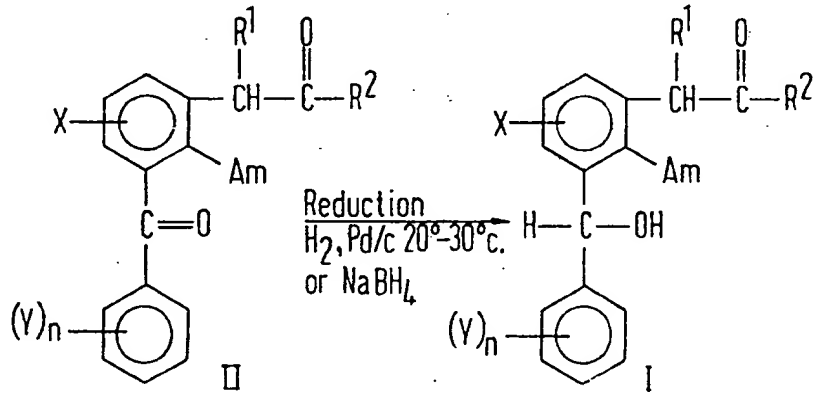
Y represents a hydrogen or a halogen atom or a loweralkyl, loweralkoxy, trifluoromethyl or -S-loweralkyl group,

M represents a pharmaceutically acceptable cation or fraction thereof when the cation is multivalent, and n is 1 to 3 inclusive.

It is, therefore, an object of the present invention to provide novel 2-amino-3-[hydroxy(phenyl)-methyl]phenylacetic acids, metal salts, hydrates, amides and esters.

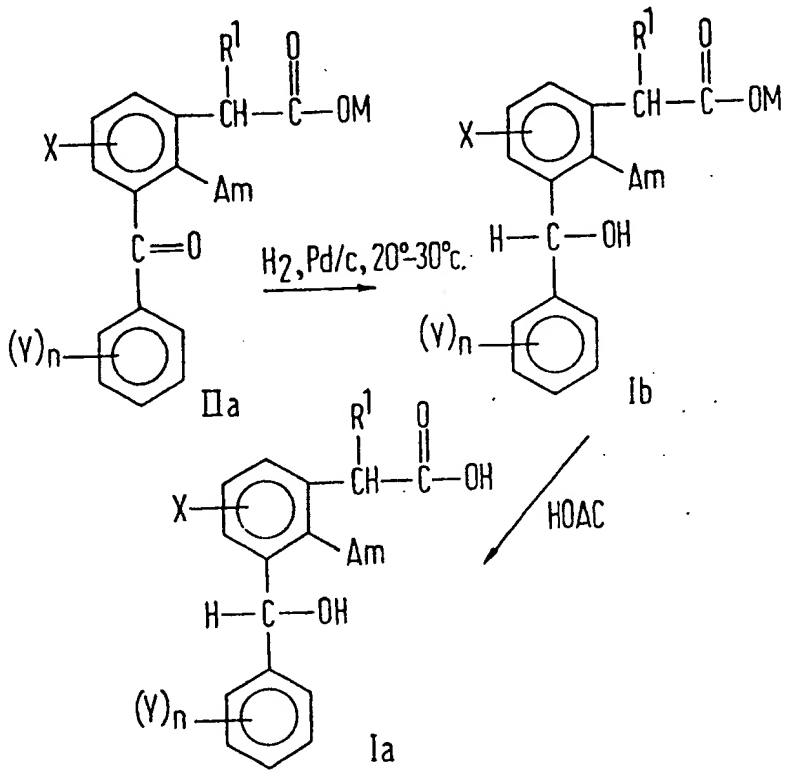
Another object is to provide a novel method for the treatment of a living animal body and especially a mammalian body for the purpose of alleviating inflammation, utilizing the 2-amino-3-[hydroxy(phenyl]methyl] phenylacetic acids and aforesaid derivatives thereof and therapeutic compositions therefor.

The 2-amino-3-[hydroxy(phenyl)methyl]phenylacetic acids and metal salts thereof, esters and amides are for the most part, with exceptions noted hereinbelow, prepared by reducing the carbonyl moiety of the starting 2-amino-3-benzoylphenylacetic acids, salts, esters and amides by an appropriate choice between reduction by hydrogenation over palladium-on-carbon and reduction with sodium borohydride as represented by the following equation:



II I

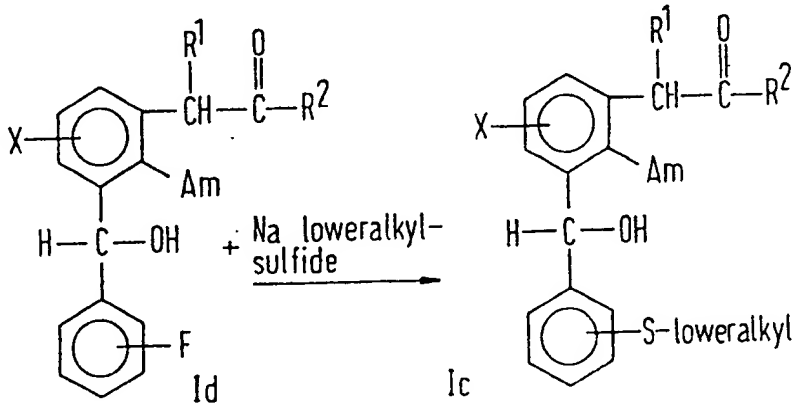
wherein R^1, R^2, X, Y, Am and n are as defined hereinabove. When R^2 represents a hydroxyl group in compounds of Formula II, hydrogenation over palladium-on-carbon causes cyclization. Sodium borohydride in double stoichiometric amount may be used in this instance; however, it is preferred to convert R^2 to a salt (OM) or its equival nt in basic solution and then hydrogenate with hydrogen over palladium-on-carbon followed by careful acidification with a weak acid such as acetic acid as represented by the following equation:



Overheating above about 30°C results in loss of a hydroxyl group to give a phenylmethyl derivative.

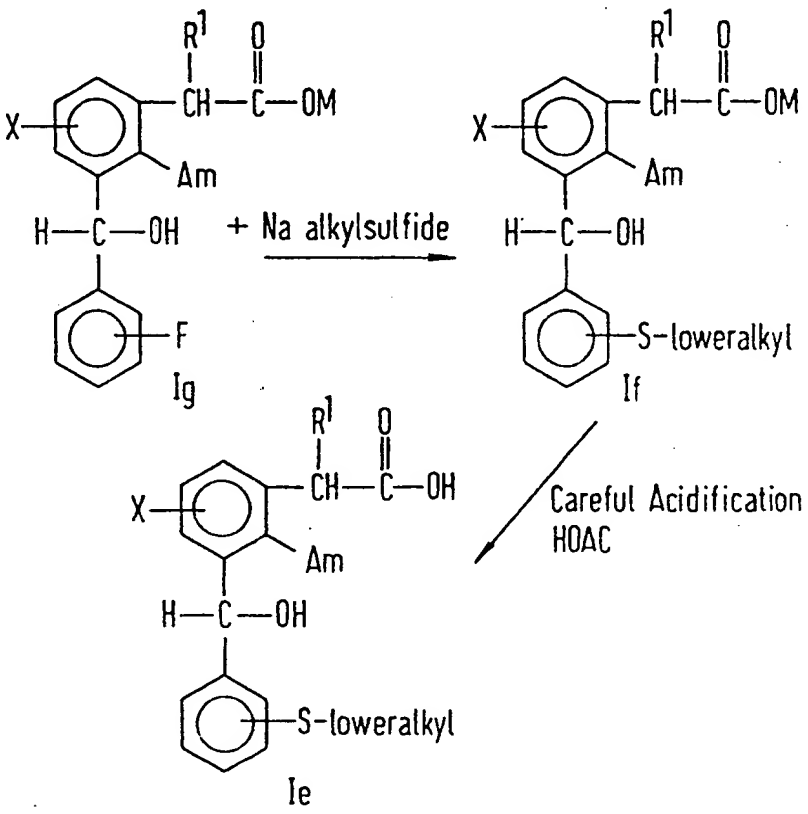
Compounds of Formula I wherein X or Y represents a halogen atom are prepared from the appropriate precursor of Formula II by reduction with sodium borohydride as hydrogenation with palladium-on-carbon causes loss of halogen.

When Y represents an -S-loweralkyl group in compounds of Formula II, hydrogenation results in loss of the -S-loweralkyl radical. Therefore, the following procedures are preferred for preparation of compounds of Formula I wherein Y represents an -S-loweralkyl group as represented by the equations starting with a compound of Formula I wherein Y represent a fluorine atom.



wherein R^1, X, and Am are as defined hereinabove and R^2 represents an -OM, O-loweralkyl or $-NR^3R^4$ group.

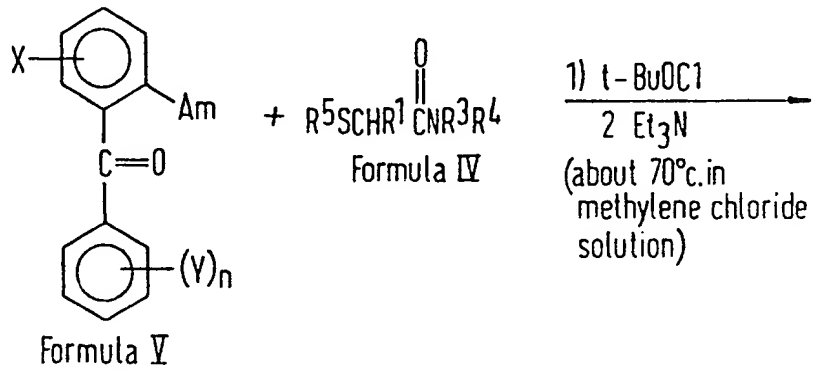
The following procedure may be used to pr pare compounds of the invention wherein R^2 represents an -OH group:

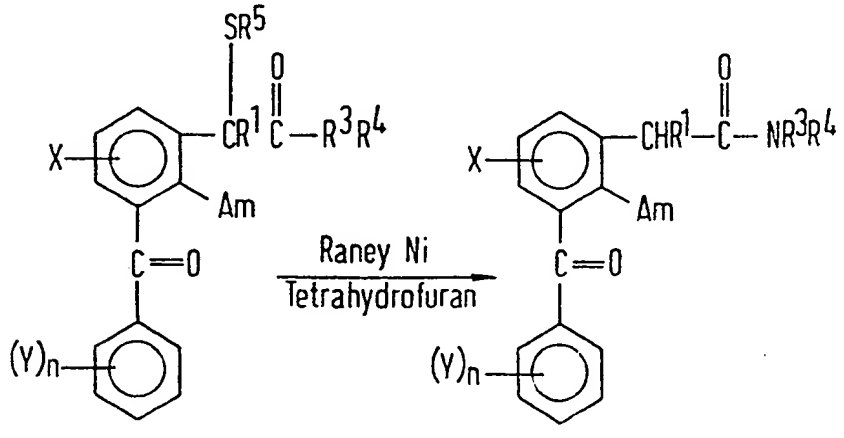


and

wherein R^1, X, Am and M are as defined hereinabove. Formulas Ia to Ig are encompassed by Formula I.

Starting materials of Formula II wherein R^2 represents an -OH, OM or -O-loweralkyl group and Am represents an $-NH_2$, or dimethylamino group may be prepared as described in U.S. Patent 4,045,576. Starting materials of Formula II wherein R^2 represents an $-NR^3R^4$ group may be prepared as disclosed in our copending British patent application No. 80.30955 according to the following equations:





wherein X, Y, n, Am, R^1, R^3 and R^4 are as hereinabove defined, except Y cannot be an -S-loweralkyl group and R^5 represents a loweralkyl or a phenyl group. The compounds of Formula IIb wherein Am is dimethylamino may be prepared by reacting compounds of Formula IIb wherein Am represents an $-NH_2$ group with formaldehyde and cyanoborohydride.

The invention may be put into practice in various ways and a number of specific embodiments will be described to illustrate the invention with reference to the accompanying preparations and examples.

Preparations 1 to 29 illustrate the preparation of compounds of Formula IIb which are starting materials for use in preparing the compounds of the invention.

Examples 1 to 9 illustrate compounds in accordance with the present invention and their preparation.

Examples 10 to 12 illustrate formulations embodying compounds of the invention and illustrate the way in which the invention can be used.

PREPARATION 1

4-[2-(Methylthioacetyl)]morpholine

A mixture of 40.2 g (0.3 mole) of ethyl methylthio-acetate and 130 g (1.5 mole) of morpholine was heated at reflux for 70 hours. Fractional distillation at reduced pressure gave 45 g (86%) of product b.p. 104-105°C/0.05 mm Hg on second distillation.

Analysis: for $C_7H_{13}NO_2S$,

Calculated:	C,47.98;	H,7.48;	N,7.99,
Found:	C,47.55;	H,7.59;	N,8.18

PREPARATION 2

2-Methylthio-N-methylacetamide

A mixture of 134 g (1.0 mol) of ethyl methylthio-acetate and 310 g (10.0 mol) of methylamine was heated in a bomb at 150°C for 72 hours. The excess amine and the ethanol produced were removed by distillation and the remaining thin syrup was distilled to give 112 g (94%) of the titled compound as a colourless liquid, b.p. 76°-78°C/0.4 mm Hg.

Analysis: for C_4H_9NOS,

Calculated:	C,40.31;	H,7.61;	N,11.75
Found:	C,39.78;	H,7.69;	N,11.88

PREPARATION 3

2-Methylthio-N,N-dimethylacetamide

A mixture of 134 g (1.0 mol) of ethyl methylthio-acetate and 360 g (8.0 mol) of dimethylamine was heated in a bomb at 150°C for 90 hours. The excess amine and the ethanol produced were removed by distillation and the residue was distilled to give 129 g (97%) of the titled compound as a clear colourless liquid, b.p. 76°-77°C/0.5 mm Hg.

Analysis: for $C_5H_{11}NOS$,

Calculated:	C,45.08;	H,8.32;	N,10.51,
Found:	C,43.88;	H,8.41;	N,10.60

PREPARATION 4

2-(2-Propylthio)acetamide

To a mixture of 46.7 g (0.5 mole) of 2-chloroacetamide in 200 ml of absolute ethyl alcohol was added in a slow stream, a solution of 38.1 g (0.5 mole) of 2-propanethiol in 100 ml of absolute ethyl alcohol and 40 g of 50% aqueous sodium hydroxide. The mixture was heated at reflux for 1 hour, then filtered. The filtrate was concentrated under reduced pressure; the residue was dissolved in methylene chloride and the solution was dried over magnesium sulphate. The mixture was filtered and the filtrate was again concentrated. On standing, the syrupy residue crystallized. Recrystallization from isopropyl ether gave 59.0 g (89%) of white platelets, melting at 52-54°C.

Analysis: for $C_5H_{11}NOS$,

Calculated:	C,45.08;	H,8.32;	N,10.51
Found:	C,45.05;	H,8.32;	N,10.55

PREPARATION 5

2-(1-Propylthio)acetamide

Utilizing the procedure of Preparation 4 but substituting an equal molar amount of 1-propanethiol for 2-propanethiol, there was obtained 61.2 g (92%) of the title compound. The white crystals melted at 49.5-51.0°C.

Analysis: for $C_5H_{11}NOS$,

Calculated:	C,45.08;	H,8.32;	N,10.51
Found:	C,44.97;	H,8.24;	N,10.40

PREPARATION 6

2-Amino-3-benzoyl-5-chloro-α-(methylthio) phenylacetamide

To a cold (−70°C) solution of 12.77 g (0.055 mole) of 2-amino-5-chlorobenzophenone in 300 ml of methylene chloride, stirred under a nitrogen atmosphere, was added 6.0 g (0.0552 mole) of t-butylhypochlorite in 20 ml of methylene chloride. After stirring for an additional 15 minutes, a suspension of 5.8 g (0.055 mole) of α-(methylthio) acetamide in 150 ml of methylene chloride was added. The mixture was stirred at −65°C for one hour. Triethylamine (5.6 g (0.055 mole)) was added and the solution was allowed to warm to room temperature. The reaction mixture was extracted with several portions of water and the organic layer dried over magnesium sulphate. The volume of solution was reduced *in vacuo* to about 200 ml and the product crystallized as a yellow solid, m.p. 173.5-174.5°C.
Yield was 6.86 g (37.3%).
Analysis: for $C_{16}H_{15}H_2O_2SCl$,

Calculated:	C,57.40;	H,4.52;	N,8.37
Found:	C,57.38;	H,4.50;	N,8.51

PREPARATION 7

2-Amino-3-benzoyl-α-(methylthio)phenylacetamide

To a cold (−70°C) solution of 19.7 g (0.10 mole) of 2-amino-benzophenone in 300 ml of methylene chloride, under nitrogen atmosphere, was added a solution of 11.5 g (0.10 mole) of 95% t-butylhypochlorite in 30 ml of methylene chloride followed after 10 minutes by a solution of 10.5 g (0.1 mole) of methylthioacetamide in 300 ml of tetrahydrofuran. The temperature was maintained at or below −55°C during these additions. After one additional hour at −60°C the mixture was allowed to warm to room temperature and the precipitate was collected by filtration. The precipitate was slurried in 200 ml of methylene chloride and 11 g (0.11 mole) of triethylamine was added. The mixture was stirred for 5 minutes. The solution was washed twice with 100 ml of water and the organic phase dried over magnesium sulphate and concentrated under reduced pressure. The residue was washed with diethylether and dried to yield 13.0 g (43%) of a light yellow powder, m.p. 153-155°C.
Analysis: for $C_{16}H_{16}N_2O_2S$,

Calculated:	C,63.98;	H,5.37;	N,9.33
Found:	C,63.64;	H,5.39;	N,9.25

PREPARATION 8

2-Amino-3-(4-chlorobenzoyl)-α-(phenylthio)-pheyl-acetamide

To a cold (−70°C) solution of 34.6 g (0.15 mole) of 2-amino-4'-chlorobenzophenone in 500 ml of methylene chloride was added 17.3 g (0.15 mole) of 95% t-butyl-hypochlorite, followed after 10 minutes by a solution of 25.0 g (0.15 mole) of phenylthioacetamide in 400 ml of tetrahydrofuran which was added over a 20 minute period. The temperature was maintained at −64°C or below during these additions. After two hours, 20 g (0.2 mole) of triethylamine was added and the mixture was allowed to warm to room temperature. The mixture was concentrated and the residue partitioned between water the methylene chloride. Material insoluble in either phase was collected by filtration washed with 20% aqueous ethanol solution and dried to yield 36 g (61%) of light yellow powder, m.p. 189-191°C.
Analysis: for $C_{21}H_{17}N_2O_2SCl$,

Calculated:	C,63.55;	H,4.32;	N,7.06
Found:	C,63.73;	H,4.36;	N,7.16

PREPARATION 9

4-[2-(2-Amino-3-benzoylphenyl)-2-(methylthio)-acetylmorpholine

To a cold (−65°C) solution of 9.9 g (0.05 mole) of 2-aminobenzophenone and 8.8 g (0.05 mole) of 4-α-methylthio)acetylmorpholine in 200 ml of methylene chloride was added dropwise a solution of 5.8 g (0.05 mole) of 95% t-butylhypochlorite in 20 ml of methylene chloride. After one additional hour at −60°C, 5.1 g (0.05 mole) of triethylamine was added and the mixture was allowed to warm to room temperature. The solution was washed twice with 100 ml of water, dried over magnesium sulphate and concentrated under reduced 5. pressure. The residue was chromatographed on 600 g of silica gel eluting first with diisopr pylether and finally with 10% acetone in diisopropylether. The eluate was concentrated, the residue dissolved in 150 ml ethanol and the solution poured into 400 ml of water. The 10. undissolved solid was collected and crystallized from diethylether and dried. Yield was 12.3 g (62%) of yellow crystals, m.p. 119-121°C.
Analysis: for $C_{20}H_{22}N_2O_3S$,

Calculated:	C,64.84;	H,5.99;	N,7.56
Found:	C,65.01;	H,5.99;	N,7.57

PREPARATION 10

2-Amino-3-benzoyl-5-chloro-a-[(4-chlorophenyl)thio]phenylacetamide

To a cold (−70°C) solution of 20 g (0.0863 mol) of 2-amino-5-chlorobenzophenone in 500 ml of methylene

hypochlorite in 50 ml of methylen chloride. After stirring for an additional 15 minutes, a solution of 17.35 g (0.0863 mole) of α-(4-chlorophenylthio)acetamide in 500 ml of a 50/50 mixture of tetrahydrofuran and methylene chloride was added. The mixture was stirr d at −70°C for 2 hours, 8.72 g (0.0863 mole) of triethylamine was added, and the stirred solution was allowed to warm to room temperature over a period of 2 hours. The reaction mixture was extracted with several portions of water and the organic layer dried over magnesium sulphate. The volume of liquid was reduced to about 500 ml. 500 ml of methylene chloride was added to precipitate the product, which after filtration and drying weighed 16.62 g (44.7%). The yellow solid melted at 198-200°C.

Analysis: for $C_{21}H_{16}N_2O_2SCl_2$,

Calculated:	C,58.48;	H,3.74;	N,6.49
Found:	C,58.49;	H,3.77;	N,6.67

PREPARATION 11

2-Amino-3-benzoyl-5-chloro-α-(phenylthio)phenylacetamide

To a cold (−70°C) solution of 80.72 g (0.349 mole) of 2-amino-5-chlorobenzophenone in 1.5 litre of methylenechloride, under nitrogen atmosphere, was added 39.1 g (0.360 mole) of t-butyl hypochlorite in 100 ml of methylene chloride. After stirring for 10 minutes a solution of 59.1 g (0.354 mole) of α-(phenylthio)-acetamide in 1.5 litre of tetrahydrofuran was added. The mixture was stirred for 1.25 hours at −65°C, 37.5 g (0.371 mole) of triethylamine was added and the solution was allowed to warm to room temperature. The reaction mixture was extracted with several portions of water and the organic layer was dried over anhydrous sodium sulphate. The volume of solution was reduced *in vacuo* and a yellow solid precipitated, which, when recrystallized from acetonitrile, was a yellow crystalline solid, m.p. 190°-191°C (d).

Analysis: for $C_{21}H_{17}N_2O_2SCl$,

Calculated:	C,63.55;	H,4.32;	N,7.06
Found:	C,63.62;	H,4.29;	N,7.08

PREPARATION 12

2-Amino-3-benzoyl-α-(phenylthio)phenylacetamide

Following the procedure of Preparation 11 but substituting equal molar amounts of 2-aminobenzophenone for 2-amino-4-chlorobensophenone the title compound was obtained in 57% yield. Recrystallized from methylene chloride-diethyletherhexane, the compound melted at 153-154°C.

Analysis: for $C_{21}H_{18}N_2O_2S$,

Calculated:	C,69.59;	H,5.01;	N,7.73
Found:	C,69.33;	H,5.00;	N,7.76

PREPARATION 13

2-Amino-3-benzoyl-α-(methylthio)-N-methylphenylacetamide

A solution of 29.6 g (0.15 mole) of 2-aminobenzophenone in 350 ml of methylene chloride was cooled to −70°C and 17.9 g (0.15 mol) of 2-methylthio-N-methyl-acetamide in 20 ml of methylene chloride was added. To the (−70°C) mixture was added dropwise a solution of 17.2 g (0.15 mole) of 95% t-butylhypochlorite in 30 ml of methylene chloride. The temperature was maintained at or below −65°C for 1.5 hours, then 15.1 g (0.15 mole) of triethylamine was added rapidly. The solution was allowed to warm to room temperature and was washed with water. The organic solution was concentrated and the residue crystallized when mixed with isopropyl ether. The solid was recrystallized from isopropyl alcohol to give 31 g (65%) of yellow needles, m.p. 149.0-150.0°C.

Analysis: for $C_{17}H_{18}N_2O_2S$,

Calculated:	C,64.94;	H,5.77;	N,8.91
Found:	C,65.24;	H,5.83;	N,8.99

PREPARATION 14

2-Amino-3-benzoyl-α-(methylthio)-N,N-dimethylphenylacetamide

A solution of 29.6 g (0.15 mole) of 2-aminobenzophenone in 350 ml of methylene chloride was cooled to −70°C and 20.0 g (0.15 mole) of 2-methylthio-N,N-dim thylac tamide was added. To the mixture (−70°C) was added dropwise a solution of 17.2 g (0.15 mole0 of 95% t-butylhypochlorite in 30 ml of methylene chloride. The temperature was maintained at or below −65°C for 1.5 hours, then 15.1 g (0.15 mole) of triethylamine was added rapidly. The solution was allow d to warm to room temperature and was washed with water. The organic solution was concentrated and the residue crystallized when mixed with isopropyl ether. The solid was recrystallized from isopropyl alcohol to give 39.8 g (81%) bright yellow crystals, m.p. 153-155°C.

Analysis: for $C_{18}H_{20}N_2O_2S$,

Calculated:	C,65.83;	H,6.14;	N,8.53
Found:	C,65.87;	H,6.15;	N,8.52

PREPARATION 15

2-Amino-3-(4-fluorobenzoyl)-α-(n-propylthio)phenylacetamide

A solution of 21.5 g (0.1 mole) of 4'-fluoro-2-aminobenzophenone in 400 ml of methylene chloride was cooled to −70°C and 11.5 g (0.1 mole) of 85% t-butyl-hypochlorite was added over a period of 15 minutes, keeping the temperature below −66°C. To this solution was added a solution of 13.3 g of 2-n-propylthio-acetamide in 50 ml of methylene chloride over a 10 minute period. The solution was stirred for 1 hour at −65° to −70°C and then allowed to warm to 0°C at which point 10.2 g (0.1 mole) of triethylamine was added. The solution was stirred for 10 minutes and then washed with water. The organic solution was dried over magnesium sulphate. After concentration under reduced pressure, the residue was crystallized from isopropyl alcohol and dried to give 19.5 g (56%) of yellow crystals melting at 140-142°C.

Analysis: for $C_{18}H_{19}N_2O_2SF$,

Calculated:	C,62.41;	H,5.53;	N,8.09
Found:	C,62.34;	H,5.58;	N,8.04

PREPARATIONS 16A TO 16D

In the same manner as given in Preparation 8,

2-amino-3-(2-fluorobenzoyl)-α-(phenylthio)phenyl-acetamide, (Preparation 16A)
2-amino-3-(4-trifluoromethylbenzoyl)-α-(phenylthio)phenylacetamide, (Preparation 16B)
2-amino-3-(2,4-dichlorobenzoyl)-α-(phenylthio)phenylacetamide, (Preparation 16C) and
2-amino-3-(2,4-difluorobenzoyl)-α-(phenylthio) phenylacetamide, (Preparation 16D)

are prepared from phenylthioacetamide, t-butyl-hypochlorite, and

2-amino-2'-fluorobenzophenone,
2-amino-4'-trifluoromethylbenzophenone,
2-amino-2',-4'-dichlorobenzophenone, and
2-amino-2',4'-difluorobenzophenone.

PREPARATION 17

2-Amino-3-benzoyl-5-chloro-α-(methylthio)-N-methylphenylacetamide

To a solution of 38.3 g (0.166 mole) of 2-amino-5-chlorobenzophenone in 1 litre of methylene chloride cooled to −70°C under an atmosphere of nitrogen was added 18.05 g (0.167 mole) of t-butylhypochlorite. The solution was stirred for 15 minutes and then a solution of 20.3 g (0.171 mole) of 2-methylthio-N-methylacetamide in 100 ml of methylene chloride was added. The solution was stirred at −70°C for 2 hours and 25 ml of triethylamine was added. While stirring, the solution was allowed to warm to room temperature followed by extraction with water and drying of the organic layer with magnesium sulphate. The volume of the solution was reduced to about 400 ml, ether was added and the solution placed in a refrigerator at about 0°C overnight. The solid which crystallized was dried under high vacuum for about 4 hours at 50°C. The weight of the product was 31.56 g (54.6%), and it melted at 170-171°C.

Analysis: for $C_{17}H_{17}N_2O_2SCl$,

Calculated:	C,58.53;	H,4.91;	N,8.03
Found:	C,58.68;	H,4.91;	N,8.13

PREPARATION 18

3-Benzoyl-2-(N-methylamino)-α-(methylthio)phenylacetamide.

When in accordance with the procedure of Preparation 7, 2-N-methylaminobenzophenone is substituted in equimolar amount for 2-aminobenzophenone, the title compound is obtained.

PREPARATION 19

2-Amino-3-benzoyl-5-chlorophenylacetamide

A mixture of 21.34 g (0.0639 mole) of 2-amino-3-benzoyl-5-chloro-α-(methylthio)-phenylacetamide and excess Raney nickel in a mixture of 900 ml of absolute ethanol and 200 ml of dimethylformamide was stirred at room temperature for 45 minutes. The mixture was filtered through Celite (R.T.M.) to remove the Raney nickel. The solvent was removed *in vacuo* to give a yellow solid which when crystallized melted at 213.5-215.0°C. (d).

Analysis: for $C_{15}H_{13}N_2O_3Cl$,

Calculated:	C,62.40;	H.4.54;	N,9.70
Found:	C,62.35;	H,4.58;	N,9.74

PREPARATION 20

2-Amino-3-benzoyl-phenylacetamide

To an agitated solution of 9.7 g (0.032 mole) of 2-amino-3-benzoyl-α-(methylthio)-phenylacetamide in 100 ml of tetrahydrofuran was added 80 g of wet Raney nickel (washed 3 times with water and 3 times with tetrahydrofuran). After 10 minutes the mixture was filtered to remov Raney nickel and the filtrate concentrated under vacuum. The residue was crystallized from isopropyl alcohol to give 6.0 g (73%) of yellow needles, m.p. 178.5-180.0°C.

Analysis: for $C_{15}H_{14}N_2O_2$,

Calculated:	C,70.85;	H,5.55;	N,11.02
Found:	C,70.53;	N,5.53;	N,11.04

PREPARATION 21

2-Amino-3-(4-chlorobenzoyl)phenylacetamide

To an agitated solution of 28.5 g (0.077 mole) of 2-amino-3-(4-chlorobenzoyl)-α-(phenylthio))phenylacetamide in one litre of tetrahydrofuran was added 230 g of wet Raney nickel (washed 3 times with water and 3 times with tetrahydrofuran). After 15 minutes the mixture was filtered and the filtrate concentrated under reduced pressure to give 17.4 g (84%) of yellow-crystalline solid. Recrystallization from isopropyl alcohol followed by recrystallizing twice from absolute ethanol gave yellow needles, m.p. 212-215°C.

Analysis: for $C_{15}H_{13}N_2O_2Cl$,

Calculated:	C,62.40;	H,4.54;	N,9.70
Found:	C,62.76;	H,4.58;	N,9.83

PREPARATION 22

4-[2-(2-Amino-3-benzoylphenyl)acetyl]morpholine

To an agitated solution of 18.5 g (0.05 mole) of 4-[2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetyl] morpholine in 300 ml of tetrahydrofuran was added 150 g of wet Raney nickel. After 15 minutes the mixture was filtered and the filtrate concentrated under reduced pressure. After recrystallization of the residue from isopropyl alcohol, there was obtained 13.3 g (82%) of bright bellow crystals, m.p. 156.5-158.5°C.

Analysis: for $C_{19}H_{20}N_2O_3$,

Calculated:	C,70.35;	H,6.22;	N,8.64
Found:	C,70.24;	H,6.21;	N,8.63

PREPARATION 23

2-Amino-3-benzoyl-N-methylphenylacetamide

A solution of 22.5 g (0.072 mole) of 2-amino-3-benzoyl-α-(methylthio)-N-methylphenylacetamide in 400 ml of tetrahydrofuran was treated with 160 g of wet Raney nickel (washed 3 times with water and 3 times with tetrahydrofuran) for 10 minutes. The mixture was filtered and the filtrate was concentrated. The residue was crystallized from isopropyl alcohol to give 17.2 g (89%) of yellow needles, m.p. 145-146°C.

Analysis: for $C_{16}H_{16}N_2O_2$,

Calculated:	C,71.62;	H,6.01;	N;10.44
Found:	C,71.76;	H,6.05;	N,10.52

PREPARATION 24

2-Amino-3-benzoyl-N,N-dimethylphenylacetamide

A solution of 33.0 g (0.1 mol) of 2-amino-3-benzoyl-α-(methylthio)-N,N-dimethylphenylacetamide in 500 ml of tetrahydrofuran was treated with 240 g of wet Raney nickel (washed 3 times with water and 3 times with tetrahydrofuran) for 10 minutes. The mixture was filtered and the filtrate was concentrated. The residue was crystallized from isopropyl alcohol to give 27.2 g (96%) of yellow needles, m.p. 123-124°C.

Analysis: for $C_{17}H_{18}N_2O_2$,

Calculated:	C,72.32;	H,6.43;	N,9.92
Found:	C,72.34;	H,6.42;	N,9.98

PREPARATION 25

2-Amino-3-(4-fluorobenzoyl)phenylacetamide

A solution of 24.2 g (0.07 mole) of 2-amino-3-(4-fluorobenzoyl)-α-(n-propylthio)phenylacetamide in 300 ml of tetrahydrofuran was treated with 250 g of wet Raney nickel (washed 3 times with water and 3 times with tetrahydrofuran). The mixture was stirred for one hour and filtered. The filtrate was concentrated under vacuum and the residue was recrystallized from 95% ethyl alcohol to give 14.8 g (78%) of yellow needles melting at 184-186°C.

Analysis: for $C_{15}H_{13}N_2O_2F$,

Calculated:	C,66.17;	H,4.81;	N,10.29
Found:	C,66.32;	H,4.81;	N,10.48

PREPARATIONS 26A TO 26D

In the same manner as given in Example 2, Preparation 25,
2-Amino-3-(2-fluorobenzoyl)phenylacetamide, (Preparation 26A)
2-Amino-3-(22,4-dichlorobenzoyl)phenylacetamide, (Preparation 26B)
2-Amino-3-(2,4-difluorobenzoyl)phenylacetamide, (Preparation 26C) and
2-Amino-3-(4-trifluoromethylbenzoyl)phenylacetamide (Preparation 26D) are prepared from
2-Amino-3-(2-fluorobenzoyl)-α-(phenylthio)phenylacetamide, (see Preparation 16A)
2-Amino-3-(2,4-dichlorobenzoyl)-α-(phenythio)-phenylacetamide, (see Preparation 16B)
2-Amino-3-(2,4-difluorobenzoyl)-α-(phenylthio)-phenylacetamide, (see Preparation 16C) and
2-Amino-3-(4-trifluoromethylbenzoyl)-α-(phenylthio)phenylacetamide. (see Preparation 16D).

PREPARATION 27

2-Amino-3-benzoyl-5-chloro-N-methylphenylacetamide

A solution of 28.33 g (0.081 mole) of 2-amino-3-benzoyl-5-chloro-α-(methylthio)-N-methylacetamide in one litre of tetrahydrofuran was treated with excess Raney nickel at room temperature for 2 hours. The solution was filtered through Celite (R.T.M.). The Raney nickel residue was washed with acetone and the wash and washings filtered. The combined organic filtrates were dried over magnesium sulphate and the volume reduced to about 300 ml. Excess ether was added and the solution allowed to stand at room temperature for one hour followed by refrigeration overnight. The yellow solid, when collected and dried, weighed 20.94 g (85.68%) and melted at 179-180°C.

Analysis: for $C_{16}H_{15}N_2O_2Cl$,

Calculated:	C,63.48;	H,4.99;	N,9.25
Found:	C,63.44;	H,4.99;	N,9.27

PREPARATION 28

3-Benzoyl-2-(N-methylamino)phenylacetamide

When in the procedure of Preparation 20, 3-benzoyl-2-(N-methylamino)-α-(methylthio)phenylacetamide is substituted for 2-amino-3-benzoyl-α-(methylthio) phenylacetamide, the title compound is obtained.

PREPARATION 29

3-Benzoyl-2-(N,N-dimethylamino)phenylacetamide

A solution of 12.7 g (0.05 mol) of 2-amino-3-benzoyl-phenylacetamide in 150 ml of acetonitrile was treated four times with 16 ml (0.2 mole) of 37% formalin, 6.4 g (0.1 mole) of sodium cyanoborohydride and 2 ml of glacial acetic acid with a 15-minute stirring period between each treatment. The mixture was finally poured into dilute sodium hydroxide and extracted three times with diethylether. The ether extracts were combined, dried over magnesium sulphate and concentrated. The product was isolated by column chromatography.

PREPARATION 30

2-Amino-3-benzoylphenylacetic Acid

A mixture of 1.0 g (0.004 mole) of 3-(3,4-dichlorobenzoyl)indolin-2-one and 30 ml of 3N sodium hydroxide was refluxed for 0.5 hour. The reaction mixture was cooled, acidified to pH 6 with 3N hydrochloric acid and the slightly acidic solution was extracted with chloroform. The chloroform extract were dried (magnesium sulphate) and concentrated to a solid. Recrystallization from ethanol-water gave 0.9 g (84.5%) of pure product which melted at 143°-145°C.

Analysis: for $C_{15}H_{13}NO_3$.

Calculated:	C,70.57;	N,5.13;	N.5.49
Found:	C,70.80;	N,5.18;	N,5.55.

PREPARATION 31

2-Amino-3-(3-methoxy-4-chlorobenzoyl)phenylacetic acid

Preparation 30 was repeated ussing an equal molar amount of 3-(3-methoxy-4-chlorobenzoyl)indolin-2-one as the starting material.

PREPARATION 32

Sodium 2-amino-3-benzoylphenylacetate Dihydrate

A mixture of 2.6 g of (2-amino-3-benzoylphenyl)-acetic acid and sodium hydroxide (0.1 mole) in 25 ml of water was stirred for approximately 10 minutes and then heated to reflux under nitrogen. The reaction mixture was then cooled and filtered. The filtrate was vaporated down to approximately 2 ml, r filtered and a large volume of acetone added to the filtrate to precipitate the product as bright yellow flakes. Yield 70%.

Analysis: for $C_{15}H_{16}NO_5Na$,

Calculated:	C,57.51;	H,5.15;	N,4.47
Found:	C,58.22;	H,4.62;	N,4.47

PREPARATION 33

2-Amino-3-benzoyl-5-chlorophenylacetic Acid Hemihydrate

A mixture of 1.5 g (0.055 mole) of 5-chloro-7-benzoylindolin-2-one in 25 ml of 3N sodium hydroxide was refluxed for 45 minutes and the resulting solution filtered and diluted with an equal volume of water. The solution was then neutralized slowly with glacial acetic acid. The resulting yellow-green precipitate was filtered off and dried in a drying pistol (no heat). The compound weighed 1.0 g (63%) and melted at 85°-87°C.

Analysis: for $C_{15}H_{12}ClNO_3 \cdot {}_{0.5}H_2O$,

Calculated:	C,60.31;	H,4.39;	N,4.69,
Found:	C,60.59;	H,4.09;	N,4.65

PREPARATION 34

Sodium 2-amino-3-(4-chlorobenzoyl)phenylacetate Hydrate

A mixture of 3.5 g (0.0125 mole) of 2-amini-3-(p-chlorobenzoyl)phenylacetic aacid in a water solution containing 0.5 g of sodium hydroxide (0.125 mole) was refluxed for 45 minutes, cooled and filtered. The filtrate was concentrated to an oily consistency and poured into a large volume of acetone. A yellow precipitate separated which was collected and identified by nuclear magnetic resonance spectrum as the desired product. The product (2.6 g) (67%) melted at 265°C (dec.) after crystallization from ethanol-ethyl ther.

Analysis: for $C_{15}H_{13}ClNO_4Na$,

Calculated:	C,54.64;	H,3.97;	N,4.24
Found:	C,55.61;	H,3.68;	N,4.31

PREPARATION 35

Ethyl 2-amino-3-(4-chlorobenzoyl)phenylacetate

Fourteen grams of sodium 2-amino-3-(4-chloro-benzoy) phenylacetate was dissolved in approximately 150 ml of dimethylformamide and the solution treated with 30 g of ethyl iodide. The solution was stirred at room temperature for 2.5 hours, the solution added to water and the mixture extracted several times with benzene. The combined benzene extracts were washed with dilute base and water, dried over sodium sulphate and concentrated to an oil which crystallized on trituration with petroleum ether (30-60). Recrystallization from absolute ethanol gave 11.6 g of yellow flakes; m.p. 101 - 102°C.

Analysis: for $C_{17}H_{16}ClNO_3$,

Calculated:	C,64.26;	H,5.08;	N,4.41
Found:	C,65.14;	H,5.06;	N,4.51

PREPARATION 36

2-Amino-3-(4-fluorobenzoyl)phenylacetic Acid

A mixture of 1.5 g (0.006 mole) of 7-(4-fluorobenzoyl) indolin-2-one in 50 ml of 3N sodium hydroxide was refluxed under nitrogen for 45 minutes. The solution was cooled, diluted with an equal volume of water, filtered, and the filtrate was extracted twice with 50 ml of ether. The aqueous basic solution was treated dropwise with glacial acetic acid until a heavy yellow precipitate formed. The precipitate was filtered off, washed thoroughly with water and air-dried. The yield was 1.1 g (68%); m.p. 136°-137°C.

Analysis: for $C_{15}H_{12}FNO_3$,

Calculated:	C,65.93;	H,4.43;	N,4.17
Found:	C,65.79;	H,4.49;	N,4.94

PREPARATION 37

Sodium-2-amino-3-benzoyl-5-methoxyphenylacetate Sesquihydrate

A suspension of 75 mg (0.27 mole) of 5-methoxy-7-benzoylindolin-2-one in 5 ml of 3N sodium hydroxide was refluxed for 2.5 hours. The resulting yellow-orange solution was cooled, diluted with several volumes of water, filtered and saturated with sodium chloride. The solution was then passed slowly through a polyethylene column (¼ inch d. × 8 inches long) containing Amberlite XAD-2 polymeric sorbent. The column was then washed with a saturated sodium chlorid solution t r mov all residual base. While attempting to wash off the sodium chloride, however, the desired product began to elute as well (as not d by following its distinctive yellow colour). A number of fractions were collected to insure removal of all the sodium chloride and as the colour began to fade from the eluate the column was finally flushed with methanol and acetone. Evaporation of this organic solution yielded (80%) a yellow solid which decomposed above 265°C and analyzed for 1.5 moles of water as confirmed by the nuclear magnetic resonance spectrum.

Analysis: for $C_{16}H_{14}NO_4 \cdot 1.5\ H_2O$,

Calculated:	C,57.49;	H,5.126;	N,4.19
Found:	C,57.63;	H,4.90;	N,4.25

PREPARATION 38

Ethyl 2-amino-3-benzoylphenylacetate

A solution of 2.5 g (0.009 mole) of the sodium salt of 2-amino-3-benzoylphenylacetic acid in 25 ml of dry dimethylformamide was treated with 5.0 g (0.035 mole) of ethyl iodide. The mixture was stirred two hours at room temperature using a magnetic stirrer. The mixture was diluted with water and the aqueous solution extracted several times with ethyl ether. The combined extracts were washed with water, dried over sodium sulphate aand concentrated under vacuum to a yellow solid. The solid was recrystallized from absolute ethanol to give 1.7 gms (61.0%) of yellow needles which melted at 77°-78°C.

Analysis: for $C_{17}H_{17}NO_3$,

Calculated;	C,72.07;	H,6.05;	N,4.94
Found:	C,72.33;	H,5,83;	N,5.07.

PREPARATION 39

Methyl 2-amino-3-benzoylphenylacetate

A solution of 4.0 g (0.014 mole) of the sodium salt of 2-amino-3-benzoylphenylacetic acid in 100 ml of dry dimethylformamide was treated with 8.0 g (0.057 mole) of methyl iodide. After stirring for two hours the solution was poured into water and the aqueous solution extracted several times with ethyl ether. The combined extracts were washed with water, dried over sodium sulphate and concentrated under vacuum to a yellow oil. The oil was crystallized from a chilled methanol-water solution to give 3.5 gms (90%) of a yellow solid which melted at 52°-54°C.

Analysis: for $C_{16}H_{15}NO_3$,

Calculated:	C,71.36;	H,5.61;	N,5.20
Found:	C,71.51;	H,5.63;	N,5.27

PREPARATION 40

Methyl 2-dimethylamino-3-benzoylphenylacetate

A stirred solution of 4.6 gms (0.0165 mole) of methyl 2-amino-3-benzoylphenylacetate and 13.2 ml (0.165 mole) of 37% formaldehyde in 66 ml of acetonitrile was treated with 3.14 gms (0.0495 mole) of sodium cyanoborohydride. Glacial acetic acid (1.65 ml) was added over a ten minute period and stirring continued for 2.0 hours at room temperature. An additional 1.65 ml of glacial acetic acid was added and the mixture stirred over a weekend (about 65 hours). The mixture was diluted with ether and the ether solution was successively washed with 3N potassium hydroxide solution, water, dried over sodium sulphate and concentrated under vacuum to give approximately 1.0 g (18%) of a yellow oil. A portion of the oil was molecularly distilled for an analytical sample.

Analysis: for $C_{18}H_{19}NO_3$,

Calculated:	C,72.71;	H,6.44;	N,4.71
Found:	C,72.33;	H,6.26;	N,4.99.

PREPARATION 41

Sodium 2-amino-3-benzoyl-α-methylphenylacetate Hydrate

A suspension of 9 g (0.036 mole) of 7-benzoyl-3-methylindolin-2-one in 100 ml of 3N sodium ydroxide was refluxed for 18 hours under nitrogen. The mixture was filtered and stripped under water pump vacuum to yield a gummy mixture of sodium hydroxide, water, and product. The mixture was triturated with boiling isopropanol and filtered. The isopropanol solution was cooled and filtered to separate the bright yellow product. The product weighed 4.0 g and melted at 218°C (dec.)

Analysis: for $C_{16}H_{14}NO_3Na$,

Calculated:	C,57.31;	H,5.41;	N,4.18
Found:	C,57.69;	H,5.12;	N,4.27

PREPARATION 42

Potassium 2-amino-3-benzoylphenylacetate Hydrate

A solution of 4.0 g (0.015% mole) of 2-amino-3-benzoylphenylacetic acid in 40 ml of tetrahydrofuran was treated with 5.06 g (0.045 mole) of 50% potassium hydroxide solution; a precipitate separated immediately. The cold solution (ice bath) was stirred for one hour under nitrogen and filtered. The dried product was r crystallized from ethanol-isopropyl ether to give 3.5 g (72%) of product as long yellow needles.

Analysis: for $C_{15}H_{12}NO_3K.H_2O$,

Calculated:	C,57.86;	H,4.53;	N.4.50
Found:	C,57.78;	N,4.47;	N,4.62.

PREPARATION 43

2-Amino-3-[4-methoxybenzoyl]phenylacetic Acid

A solution of sodium methoxide maintained under nitrogen (2.27 g of sodium in 25 ml of methanol) was treated successively with 50 ml of benzene and 3.4 g (0.013 mole) of 7-(4-fluorobenzoyl)indolin-2-one. The mixture was refluxed for 4 hours. The mixture was concentrated and the residue was treated with 100 ml of

with 100 ml of water and filtered. The filtrate was washed three times with 60ml of ether, treated with charcoal and filtered. The filtrate was then treated dropwise with glacial ac tic acid giving a yellow precipitate which was filtered off, washed thoroughly with water and air-dried. The yield was 2.5 g (66%); m.p. 117°-118°C.

Analysis: for $C_{16}H_{15}NO_4$,

Calculated:	C,67.36;	H.5.30;	N,4.91
Found:	C,67.25;	H,5.18;	N,4.99.

The following Examples 1 to 9 illustrate the compounds of the invention.

EXAMPLE 1

2-Amino-3-[hydroxy(phenyl)methyl]phenylacetic Acid Hydrate [1:1]. (R^1=H; R^2=OH; Am=NH_2; X=Y=H)

To a stirred solution of 2 g (0.0072 mole) of sodium 2-amino-3-benzoylphenylacetate dihydrate (see Preparation 32) in 25 ml of water was added 25 ml of 3N sodium hydroxide followed by 0.285 g (0.0075 mole) of sodium borohydride. The resulting yellow solution was stirred for 18 hours during which time the solution lightened in colour considerably. The solution was filtered, cooled and neutralized slowly with glacial acetic acid. The white precipitate obtained weighed 1.3 g (65%), m.p. sintering at 115°C and melting at 160°C.

Analysis: for $C_{15}H_{17}NO_4$,

Calculated:	C,65.44;	H,6.22;	N,5.09
Found:	C,65.13;	H,6.21;	H,5.08.

EXAMPLE 2

Sodium 2-Amino-3-[hydroxy(phenyl)methyl]phenylacetate. (R^1=H; R^2=OM; M=Na; Am=NH_2; X=Y=H)

A solution of 14.8 g (0.05 mole) of sodium 2-amino-3-benzoylphenylacetate monohydrate (see Preparation 32) in 250 ml of tap water was hydrogenated over 10% palladium-on-charcoal at ambient temperature overnight. The mixture was filtered through Celite (R.T.M.) and the filtrate concentrated under reduced pressure. The residue was crystallized with the aid of chasing with three 50 ml portions of absolute ethanol to give a white solid. The solid was recrystallized from methanol-diethyl-ether and ethanol-water to yield 7.0 g (53%) of white solid, m.p. 273°C.

Analysis: for $C_{15}H_{14}NO_3Na$,

Calculated:	C,64.51;	H,5.05;	N,5.02
Found:	C,64.37;	H,5.07;	N,5.03.

EXAMPLE 3

2-Amino-5-chloro-3-[hydroxy(phenyl)methyl]phenylacetic Acid. (R^1=H; R^2=OH; AM=NH_2; X=Cl; Y=H)

To a stirred solution of 12.58 g (0.04 mole) of sodium 2-amino-3-benzoyl-5-chlorophenylacetate (see preparation 33) in 100 ml of water was added 100 ml of 3N sodium hydroxide followed by 1.6 g (0.04 mole) of sodium borohydride. The mixture was stirred for 3 hours until it became a clear orange coloured solution. The solution was neutralized with acetic acid which was collected by filtration, washed with water and dried. Cream coloured solid 10.2 g (79.%), m.p. 134°(d) was obtained.

Analysis: for $C_{15}H_{14}ClNO_3$,

Calculated:	C,61.76;	H,4.84;	N,4.80
Found:	C,61.69;	H,4.81;	N,4.76.

EXAMPLE 4

Sodium-2-amino-3-[hydroxy(4-chlorophenyl)methyl]-phenylacetic Acid Hydrate [4:1]. (R^1=H; R^2=OH; Am=NH_2; X=H; Y=Cl)

A mixture of 9.0 g (0.029 mole) of sodium 2-amino-3-(4-chlorobenzoyl)phenylacetate monohydrate (see preparation 34) in 200 ml of water and 100 ml of 2% aqueous sodium hydroxide solution was filtered through Celite (R.T.M.) and the filtrate was treated with 1.1 g (0.03 mole) of sodium borohydride. The mixture was stirred at ambient temperature for 3 hours and filtered again through Celite (R.T.M.). The filtrate was acidified with acetic acid (foaming). The resulting white solid was collected by filtration and washed with water. The solid was stirred in a solution of 150 ml and 1.1 g (0.03 mole) of sodium hydroxide. The solution was filtered and the filtrate titrated to pH 8.5 with 15% hydrochloric acid solution. After standing at ambient temperature overnight, the mixture was filtered through Celite (R.T.M.) and the filtrate concentrated under reduced pressure. The residue was crystallized with the aid of absolute ethanol to produce a white solid which recrystallized from water and, when dried, weighed 4.2 g (47%), m.p. 138°(d).

Analysis: for $C_{15}H_{13}ClNO_3Na$,

Calculated:		H,4.28;	N,4.42
Found:	C,56.62;	H,4.28;	N,4.40;

EXAMPLES 5A TO 5F

When in accordance with the procedure of Example 1, equal molar amounts of the following are substituted for sodium 2-amino-3-benzoylphenylacetate dihydrate

Sodium 2-amino-3-benzoyl-5-chlorophenylacetate, (see Preparation 33),

Sodium 2-amino-3-(4-chlorobenzoyl)phenylacetate hydrate, (see Preparation 34),

Ethyl 2-amino-3-(4-chlorobenzoyl)phenylacetate, (see Preparation 35),

Sodium 2-amino-3-(4-fluorobenzoyl)phenylacetate, (see Preparation 36),

Sodium 2-amino-3-(3,4-dichlorobenzoyl)phenylacetate, (see Preparation 30),

Sodium 2-amino-3-(3-methoxy-4-chlorobenzoyl) phenylacetate, (see Preparation 31), there are obtained

2-Amino-3-[hydroxy(phenyl)methyl]-5-chlorophenyl acetic acid, (Example 5A; R^1=H; R^2=OH; Am=NH_2; X=Cl; Y=H),

2-Amino-3-[hydroxy(4-chlorophenyl)methyl]phenyl acetic acid, (Example 5B; R^1=H; R^2=OH; Am>NH_2; X=H; Y=Cl; n=1),

Ethyl 2-amino-3-[hydroxy(4-chlorophenyl)methyl] phenylacetate, (Example 5C; R^1=H; R^2=O-Et; Am=NH_2; X=H; Y=Cl; n=1),

2-Amino-3-[hydroxy(4-fluorophenyl)methyl]phenyl acetic acid, (Example 5D; R^1=H; R^2=OH; Am=NH_2; X=H; Y=F; n=l),

2-Amino-3-[hydroxy(3,4-dichlorophenyl)methyl] phenyl acetic acid, (Example 5E; R^1=H; R^2=OH; Am=NH_2; X=H; Y=Cl; n=2),

2-Amino-3-[hydroxy(3-methoxy-4-chlorophenyl)methyl]phenylacetic acid, (Example 5F; R^1=H; R^2=OH; Am=NH_2; X=H; Y=OCH_3 and Cl; n=2).

EXAMPLES 6A TO 6G

When in accordance with the procedure of Example 2, equal molar amounts of the following are substituted for sodium 2-amino-3-benzoylphenylacetate monohydrate

Sodium 2-amino-3-benzoyl-5-methoxyphenylacetate sesquihydrate, (see Preparation 37),

Ethyl 2-amino-3-benzoylphenylacetate, (see Preparation 38),

Methyl 2-amino-3-benzoylphenylacetate, (see Preparation 39),

Methyl 2-dimethylamino-3-benzoylphenylacetate, (see Preparation 40),

Sodium 2-amino-3-benzoyl-α-methylphenylacetate hydrate, (see Preparation 41),

Potassium 2-amino-3-benzoylphenylacetate hydrate, (see Preparation 42),

Sodium 2-amino-3-(4-methoxybenzoyl)phenylacetate, (see Preparation 43),

there are obtained

2-Amino-3-[hydroxy(phenyl)methyl]-5-methoxyphenylacetic acid (Example 6A; R^1=H; R^2=OH; Am=NH_2; X=OCH_3; Y=H),

Ethyl 2-amino-3-[hydroxy(phenyl)methyl]phenylacetate, (Example 6B; R^1=H; R^2=OEt; Am=NH_2; X=OCH_3; Y=H),

Methyl 2-amino-3-[hydroxy(phenyl)methyl]phenylacetate, (Example 6C; R^1=H; R^2=OCH_3; Am=NH_2; X=H; Y=H),

Methyl 2-dimethylamino-3-[hydroxy(phenyl)methyl]phenylacetate, (Example 6D; R^1=H; R^2=OCH_3; Am=$N(CH_3)_2$;

2-Amino-3-[hydroxy(phenyl)methyl]phenylacetic acid, (Example 6E; R^1=H; R^2=OH; Am=NH_2; X=H; Y=H),

2-Amino-3-[hydroxy(phenyl)methyl]phenylacetic acid, (Example 6F; R^1=H; R^2=OH; Am=NH_2; X=H; Y=H),

2-Amino-4-[hydroxy(4-methoxyphenyl)methyl] phenylacetic acid, (Example 6G; R^1=H; R^2=OH; Am=NH_2; X=H; Y=OCH_3; n=1).

EXAMPLES 7A TO 7L

When in accordance with the procedure of Example 1, equal molar amounts of the following are substituted for sodium 2-amino-3-benzoylphenylacetate:

2-Amino-3-benzoyl-5-chlorophenylacetamide, (see Preparation 19),

2-Amino-3-benzoyl-phenylacetamide, (see Preparation 20),

4-[2-(2-Amino-3-benzoylphenyl)acetyl] morpholine, (see Preparation 22),

2-Amino-3-benzoyl-N-methylphenylacetamid , (see Preparation 23),

2-Amino-3-benzoyl-N,N-dimethylphenylacetamide, (see Preparation 24),

2-Amino-3-(4-fluorobenzoyl)phenylacetamide, (see Preparation 25),

2-Amino-3-(2-fluorobenzoyl)phenylacetamide, (see Preparation 26A),

2-Amino-3-(2,4-dichlorobenzoyl)phenylacetamide, (see Preparation 26B),

2-Amino-3-(2,4-difluorobenzoyl)phenylacetamide, (see Preparation 26C),

2-Amino-3-(4-trifluoromethylbenzoyl)phenylacetamide, (see Preparation 26D),

2-Amino-3-benzoyl-5-chloro-N-methylphenylacetamide, (see Preparation 27),

3-Benzoyl-2-(N,N-dimethylamino)phenylacetamid , (see Preparation 29),

there are obtained

$R^3=R^4=H$; Am=NH_2; X=Cl; Y=H);
2-Amino-3-[hydroxy(phenyl)methyl]phenylacetamide, (Example 7B; $R^1=H$; $R^2=NR^3R^4$; $R^3=R^4=H$; Am=NH_2; X=H; Y=H),
4-2-2-Amino-3-[hydroxy(phenyl)methy] acetyl morpholine, (Example 7C; $R^1=H$; R^2=morpholine; Am=NH_2; X=H; Y=H),
2-Amino-3-[hydroxy(phenyl)methyl]-N-methylphenyl acetamide, (Example 7D; $R^1=H$; $R^2=NR^3R^4$; $R^3=CH_3$; $R^4=H$; Am=NH_2; X=H; Y=H),
2-Amino-3-[hydroxy(phenyl)methyl]-N,N-dimethylphenyl acetamide, (Example 7E; $R^1=H$; $R^2=NR^3R^4$; $R^3=R^4=CH_3$; Am=NH_2; X=H; Y=H),
2-Amino-3-[hydroxy(4-fluorophenyl)methyl]phenyl acetamide, (Example 7F; $R^1=H$; $R^2=NR^3R^4$; $R^3=R^4=H$; Am=NH_2; X=H; Y=F; n=I),
2-Amino-3-[hydroxy(2-fluorophenyl)methyl]phenyl acetamide, (Example 7G; $R^1=H$; $R^2=NR^3R^4$; $R^3=R^4=H$; Am=NH_2; X=H; Y=F; n=I),
2-Amino-3-[hydroxy(2,4-dichlorophenyl)methyl] phenyl acetamide, (Example 7H; $R^1=H$; $R^2=NR^3R^4$; $R^3=R^4=H$; Am=NH_2; X=H; Y=Cl; n=2),
2-Amino-3-[hydroxy(2,4-difluorophenyl)methyl]phenyl acetamide, (Example 7I; $R^1=H$; $R^2=NR^3R^4$; $R^3=R^4H$; Am=NH_2; X=H; Y=F; n=2),
2-Amino-3-[hydroxy(4-trifluoromethylphenyl)methyl] phenylacetamide, (Example 7J; $R^1=H$; $R^2=NR^3R^4$; $R^3=R^4=H$; Am=NH_2; X=H; Y=CF_3; n=1),
2-Amino-3-[hydroxy(phenyl)methyl]-5-chloro-N-methyl phenylacetamide, (Example 7K; $R^1=H$; $R^2=NR^3R^4$; $R^3=CH_3$; $R^4=H$; Am=NH_2; X=Cl; Y=H),
2-(N,N-dimethylamino)-3-[hydroxy(phenyl)methyl] phenylacetamide, (Example 7L; $R^1=H$; $R^2=NR^3R^4$; $R^3=R^4=H$; Am=$N(CH_3)_2$; X=H; Y=H).

EXAMPLE 8

Sodium 2-amino-2-[hydroxy(4-methylthiophenyl)methyl] phenylacetate. ($R^1=H$; R^2=OM; M=Na; Am=NH_2; X=H; Y=SCH_3; n=I)

The title compound is prepared by preparing a solution of 2-amino-3-[hydroxy(4-fluorophenyl)methyl]phenylacetic acid and an equivalent amount of sodium hydroxide and refluxing in ethanol with excess methyl mercaptide and isolation by suitable means.

EXAMPLE 9

2-Amino-3-[hydroxy(4-methylthiophenyl)methyl]phenyl acetamide. ($R^1=H$; $R^2=NR^3R^4$; $R^3=R^4=H$; Am=NH_2; X=H; Y=SCH_3; n=I)

The title compound is prepared by refluxing 2-amino-3-[hydroxy(4-fluorophenyl)methyl]phenylacetamide with excess sodium methyl mercaptide in ethanol and isolation by suitable means.

The present invention also contemplates novel therapeutic compositions containing the compounds of the invention as active ingredients. Effective quantities of any of the foregoing pharmacologically active compounds may be administered to a living animal body in any one of various ways, for example, orally as in capsules or tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intravenously in the form of sterile solutions. In forming the novel compositions of this invention, the active ingredient is incorporated in a suitable carrier, illustratively, a pharmaceutical carrier. Suitable pharmaceutical carriers which are useful in formulating the compositions of this invention include starch, gelatin, glucose, magnesium carbonate, lactose, and malt. Liquid compositions are also within the purview of this invention and suitable liquid pharmaceutical carriers include ethyl alcohol, propylene glycol, glycerine, and glucose syrup.

The pharmacologically active compounds may be advantageously employed in a unit disage of from 0.1 to 250 milligrams or more depending on the size of the animal. For example, a large animal such as a horse may require tablets of 500-1000 mg active ingredient. The unit dosage may be given a suitable number of times daily so that the daily dosage may vary from 0.3 to 450 milligrams. Five to 25 milligrams appears optimum per unit dose.

It is only necessary that the active ingredient constitute an effective amount, i.e., such that a suitable effective dosage will be obtained consistent with the dosage form employed. The exact individual dosages as well as daily dosages will, or course, be determined according to standard medical principles under the direction of a physician or veterinarian.

The active agents of the invention may be combined with other pharmacologically active agents, or with buffers, antacids or the like, for administration and the pr portion of the active agent in th compositions may be varied widely.

The following are examples of compositions formed in accordance with this invention.

EXAMPLES 10A TO 10D

Capsules of 5 mg (Example 10A), 25 mg (Example 10B) and 50 mg (Example 10C) of active ingredient per capsule are prepared. With the higher amounts of active ingredient, adjustment may be made in the amount

Typical blend for encapsulation	*Per capsule mg*
Active ingredient	5.0
Lactose	296.7
Starch	129.0
Magnesium stearate	4.3
Total	435.0 mg

Additional capsule formulations preferably contain a higher dosage of active ingredient and are as follows.

EXAMPLE 10D

Ingredients	*Per capsule mg*
Active ingredient	25.0
Lactose	306.0
Starch	99.2
Magnesium stearate	4.3
Total	435.0 mg

In each case the selected active ingredient is uniformly blended with lactose, starch, and magnesium stearate and the blend is then encapsulated.

EXAMPLE 11

A typical formulation for a tablet containing 5.0 mg of active ingredient per tablet follows. The formulation may be used for other strengths of active ingredient by adjustment of weight of dicalcium phosphate.

	Per tablet, mg
(1) Active ingredient	5.0
(2) Corn starch	13.6
(3) Corn starch (paste)	3.4
(4) Lactose	79.2
(5) Dicalcium phosphate	68.0
(6) Calcium stearate	0.9
	170.1 mg

Ingredients 1, 2, 4 and 5 are uniformly blended. A 10 percent paste in water of ingredient 3 is prepared. The blend is granulated with the starch paste and the wet mass is passed through an eight mesh screen. The wet granulation is dried and sized through a twelve mesh screen. The dried granules are blended with the calcium stearate and pressed.

EXAMPLE 12

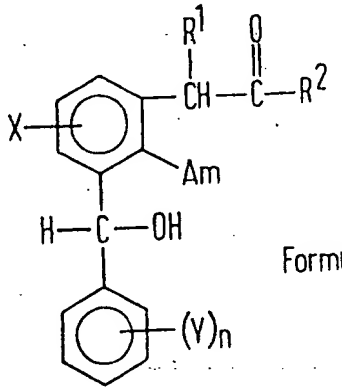
This is an example of an injectable 2% sterile solution.

	Per cc.
Active ingredient	20 mg
Preservative, e.g.	
chlorobutanol	0.5% wt./vol.
Water for injection	q.s.

The solution is prepared and clarified by filtration, filled into vials which are sealed and autoclaved.

CLAIMS

1. A compound having the formula:



Formula I

wherein:

R^1 represents a hydrogen atom or a loweralkyl group;

R^2 represents an -OH, -OM, -O-loweralkyl or $-NR^3R^4$ group;

R^3 and R^4 represent a hydrogen atom or a loweralkyl, cycloalkyl or phenyl group or a phenyl group substituted by one or more loweralkyl, loweralkoxy, or trifluoromethyl groups or halogen atoms, and R^3 and R^4 taken together with the adjacent nitrogen atom may form a heterocyclic residue;

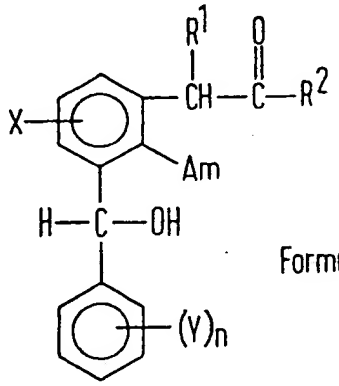
M represents a pharmaceutically acceptable cation or a fraction thereof when the cation is multivalent.

Am represents a primary amino ($-NH_2$) group, or a dimethylamino group;

X represents a hydrogen or a halogen atom or a loweralkyl or trifluoromethyl group;

Y represents a hydrogen or a halogen atom or a loweralkyl, loweralkoxy, trifluoromethyl or methylthio group and n is 1 to 3 inclusive, and when n is greater than one, Y may be the same or different, and hydrates thereof.

2. A compound having the formula:



Formula I

wherein:

R^1 represent a hydrogen atom or a methyl group;

R^2 represent an -OH, -OM, or -O-loweralkyl group;

Am represents an $-NH_2$ or dimethylamin group;

X represents a hydrogen or a halogen atom or a loweralkyl or a trifluoromethyl group;

Y represents a hydrogen or a halogen atom or a loweralkyl, loweralkoxy, trifluoromethyl or -S-loweralkyl group;

M represents a pharmaceutically acceptable cation or fraction thereof when the cation is multivalent, and n is 1 to 3 inclusive.

3. 2-Amino-3-[hydroxy(phenyl)methyl]phenylacetic acid.

4. 2-Amino-3-[hydroxy(phenyl)methy] phenylacetic acid hydrate [1:1].

5. Sodium 2-amino-3-[hydroxy(phenyl)methyl]phenylacetate.

6. 2-Amino-5-chloro-3-[hydroxy(phenyl]methyl]phenylacetic acid.

7. 2-Amino-3-[hydroxy(4-chlorophenyl)methyl]phenylacetic acid.

8. Sodium 2-amino-3-[hydroxy(4-chlorophenyl)methyl]phenylacetate hydrate [4:1].

9. A compound as claimed in Claim 1 substantially as specifically described herein with reference to any one of Examples 1 to 9.

10. A compound as claimed in Claim 1 substantially as specifically described herein with reference to any one of Examples 1 to 9 and Preparations 1 to 29.

11. A therapeutic composition suitable for alleviating inflammation in a living animal body comprising (a) an effective amount of a compound as claimed in any one of Claims 1 to 10, and (b) a pharmaceutically acceptable diluent or carrier therefor.

12. A therapeutic composition as claimed in Claim 11 substantially as specifically described herein with reference to any one of Examples 10 to 12.

13. A compound as claimed in any one of Claims 1 to 10 for use in alleviating inflammation in a living animal body.

14. A compound as claimed in any one of Claims 1 to 10 for use in producing an analgetic effect in a living animal body.

15. A compound as claimed in any one of Claims 1 to 10 for use in producing an inhibitory effect on blood platelet aggregation.

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